

Atopic eczema. What has caused the epidemic in industrialised countries and can early intervention modify the natural history of atopic eczema?

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Summary

Atopic eczema (AE) has a lifetime prevalence of between 15 and 20% in industrialized countries, but a very low prevalence in rural Africa. The 'atopic eczema epidemic' has developed in industrialized countries within the last four decades. The disease has a strong genetic influence, so environmental factors must be responsible for the dramatic increase in disease prevalence. It is therefore fair to consider what interventions may change its prevalence. In this article, several factors are considered: the increased number of doctors in industrialized countries, the development of drugs like topical steroids and emollients, the 'demanding parents' and 'old mother' syndromes, introduction of vaccination programmes, allergen exposure, breastfeeding and the possible beneficial effects of probiotics.

In 90% of children with AE, onset is before the age of 5. Its course runs over years. Approximately two out of three outgrow the disease between 7 and 12 years of age. Although its cause is unknown, type I allergic reactions are common and allergen avoidance has been attempted in many studies as a preventive measure in atopic dermatitis. However, results are rather disappointing.

The use of probiotics, i.e. daily intake of *Lactobacillus*, has proven effective in preventing, or at least delaying, the development of atopic eczema. So has breastfeeding, although some studies cannot confirm its beneficial effect. Therapeutic interventions using antihistamines, desensitisation and control of skin inflammation using topical steroids have not proven successful in shortening the course of atopic eczema, although controlled studies are lacking. The use of emollients has, however, a documented effect in up to one of three children with mild atopic eczema. It will be interesting to observe if the new topical immuno-modulators, tacrolimus and pimecrolimus, may be able to shorten the natural course of the disease.

Keywords: allergen avoidance, breastfeeding, cosmetics, diet, pimecrolimus, probiotics, tacrolimus, topical steroids

Introduction

Figure 1(a) shows an 18-month old girl, who, at the age of 12 months had her first measles-mumps-rubella (MMR) vaccination. Shortly after, she developed an itchy rash diagnosed as atopic dermatitis. Over a 9-month period, she was treated with emollients and hydrocortisone

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Figure 1 The pictures show the same girl at age 18 months (a) with atopic eczema and at age 6 years (b), when she had outgrown her disease.

acetate 1% leading to the control of symptoms. The family was contacted some years later to follow-up on her disease, and they reported that the eczema had gone, when she was about 2.5 years old. She had no relapse whatsoever, and Fig. 1(b) shows her at 6 years of age with normal looking skin, no signs of dryness or atopic stigmata. She did not develop asthma or hay fever symptoms. She had outgrown her disease. The only early interventions in this little girl were emollients and mild topical steroids. Neither diets nor allergen avoidance was tried.

This tells us that atopic eczema (AE) is not a life-sentence and Table 1 shows three studies among many indicating

Table 1 The table shows prevalence of atopic eczema in three major European studies among children age 2–16 years. When comparing lifetime prevalence with 1-year prevalence (eczema during the year prior to the time of investigation), and point prevalence (eczema at time of investigation) it is clearly seen how eczema disappears over time in most children and that it is a relapsing disease.

	Scotland	Denmark	Italy
Year of publication	1996	2001	2003
Lifetime prevalence	n.a.	21.3%	15.2%
1-year prevalence	8.1%	6.7%	n.a.
Point prevalence	2.5%	3.6%	5.8%
Age range	2–11 year	12–16 year	9 year
Number of children	n.a.	1.501	1.369
Reference	1	2	3

this.^{1–3} Also, a prospective study on antihistamines in AE showed that even placebo-treated children had a significant reduction in clinical disease activity over an 18 months period.⁴ Most children will have their eczema for months to years, often as a relapsing eczema, where the initiating factor(s) very often seems obscure to the parents. Many parents/patients know that contact with certain allergens as grass pollen, animal hair, etc. can worsen or even initiate eczema. But more often than that, relapses are unpredictable

Early intervention can mean several things: early therapeutic intervention is treatment of the acute eczema, which can be controlled in most patients with the available medications today. Early prophylactic intervention is hindrance of disease relapse using daily emollients or even the use of topical steroids or the new class of topical immunomodulators, which will prevent or reduce outbreaks of eczema. Figure 2(a) and (b) show a 2 year-old-boy, where even potent topical steroid couldn't control his severe eczema. Tacrolimus controlled it completely and the necessity to use tacrolimus became less and less. One year later, the patient is now in full control of his eczema with very little use of tacrolimus.

Finally, the most important question is, whether early intervention – by any means – can shorten the course of AE. This article discusses that.

Development of atopic eczema

AE is the first of the atopic diseases to clinically manifest. It happens at a time when the child's immune system meets the environment and undergoes immunological education. The disease is to a large extent determined by as yet unknown genetic factors, which determines that the establishment of the peripheral T-lymphocyte



Figure 2 The pictures show a boy almost 2 years of age with eczema (a) since within the first year of life. Topical steroids were ineffective but tacrolimus almost cleared his skin within 3 weeks therapy and (b) over the last year it is fully controlled on tacrolimus once or twice weekly.

immune system is skewed towards a Th-2 profile in many children.⁵ This creates the background for the frequent development of type I immunological reactions – something that is definitely more common in atopic children than their nonatopic counterparts. However, weak type I immunological reactions to environmental

allergens are also common in infants up to the age of 18 months, who do not have or develop AE.⁶ The early type I allergies are often transient.

Epidemiological studies have clearly documented an epidemic of AE and other atopic diseases in the developed world. In contrast, AE is hardly present in rural Africa.⁷ What factors could contribute to an epidemic of a largely genetically determined disease? If such factors could be defined, this would create an option for better intervention leading to a significant reduction of AE.

A number of factors are listed, which could contribute to the atopic eczema epidemic seen in industrialized countries (Table 2). All relations shown in Table 2 are likely to show a statistical correlation with the increase of atopic eczema. But, whether there is any causal relationship is unknown. Each item is discussed below.

Increased number of doctors

Industrialized countries have more doctors today than four decades ago. The playwright Eugene Ionesco is claimed to have said: 'The more doctors, the more diseases'. and there is a truth in that. In Japan, it is compulsory to have a child examined by a doctor at the age of 18 months and 3 years. In most countries, health nurses visit the families and children are seen by family doctors, when having vaccinations, as most do. Therefore, even mild cases of eczema will be recognized.

Academic and/or demanding parents

Nowadays, most women obtain an education and will have their own job. Thus, at my university (Aarhus University) the percentage of female medical students was 15% in 1965. Today, 55% of medical students are females. As a consequence of female education, the average age of first-time mothers has risen from 23 years in the 1960s to approximately 30 years today. This has happened in all industrialized countries. The number of children in a family is two or even less. All these mean higher social class, older mothers, and fewer children per family. This is the background for demanding parents who will recognize even dry skin and eventually bring the child to the doctor. The focus on allergy in the media also brings extra demands from parents, e.g. when their child has bouts of vomiting together with a rash or wheezing from one of the many respiratory infections often contracted in kindergarten schools, etc.

It is a favourite hypothesis of this author that one significant contribution to the eczema epidemic could be the 'old mother syndrome'. It is known from Down's syndrome that older mothers run a higher risk of having

Table 2 Factors which may have contributed to the rise in the prevalence of atopic eczema in industrialized countries.

Increase of doctors and dermatologists leading to increased recognition of atopic eczema	The health systems of developed countries have improved considerably. All children are seen by doctors and nurses in connection with vaccinations. This leads to increased recognition of eczema, especially mild cases.
Academic and/or demanding parents	Nowadays, both parents are educated and work, economic conditions are better with fewer children per family, and there is higher alertness to skin symptoms – including 'the old mother syndrome'.
Improvement of housing facilities and use of cosmetics	Housing has improved with better facilities such as more bathrooms, more showering, more 'cleanliness' and increased use of 'cosmetics'.
The pharmaceutical industry	Cosmetic and pharmaceutical companies have developed new remedies for treatment and control of abnormal skin physiology (emollients) and skin inflammation (topical steroids). New treatments mean increased awareness of the diseases that the products can treat, favouring increased rates of diagnosis.
Developed health systems with prophylactic intervention towards common infections among children	Today's children in developed countries are less exposed to bacterial infections, are vaccinated to avoid potential dangerous infections, and are treated with antibiotics more frequently.
The food industry development	Industrially prepared food items, sterilized food plus a large range of 'food additives including colours or taste compounds'.
The introduction of topical steroids in the 1960s	The use of topical steroids became prominent in the 1960s, at the time when the eczema epidemic started.

children with triple 21 chromosomes. Prolonged gestation correlates with a rising risk of the foetus later developing AE during its childhood.⁸ Also, second born children have significantly more eczema than first born children⁹ indicating that children of older mothers have an increased risk of having eczema. It should be stressed, however, that the age of mothers having a child developing AE later was not significantly different from mothers having non-atopic children.⁸ But the age of mothers have increased significantly in all industrialized countries.

Improvement of housing facilities and increased use of cosmetics

No doubt housing has improved in industrialized countries. This goes for larger housing with less crowded conditions, carpets, indoor climate with higher temperatures and humidity, and better bath facilities. Some dermatologists claim people are washing themselves dry of lipids, and a new prospective study indicates how 'cosmetics' often induce irritative skin reactions especially among atopics.¹⁰ A recent study in Nottingham could demonstrate that the prevalence of atopic eczema was higher in areas with high calcium content in the water, i.e. using more soap and shampoo.¹¹

The pharmaceutical industry

Any magazine on fashion and beauty tells of wonderful new emollients and shampoos that will do wonders for the appearance. The pharmaceutical industry will convince both doctors and patients of their wonder drugs¹² raising

awareness of the diseases, which the new drugs will treat. This leads to increased diagnosis of those diseases.

The new development of drugs is very important for any doctor, and it has been impressive to see, how the pharmaceutical industry today is able to cope with diseases. It took almost 500 years to come up with the cure for syphilis, but the HIV epidemic was challenged within a few years and a cure will likely be available within the next decade. So is the experience with severe acute respiratory syndrome (SARS).

The pharmaceutical industry must have customers, i.e. patients. Just consider obesity, increased blood lipids, and Alzheimer's disease – not treated 20 years ago, but today an intense focus for drug development.

Prophylactic interventions with vaccinations

Children today are vaccinated to avoid dangerous infections. Smallpox has been eradicated. The exposure to *Mycobacterium tuberculosis* has diminished dramatically in industrialized countries. It is known that this can change the development of the immune system, so Th-2 reactions become more prominent.¹³ The authors observed that atopic eczema is slightly, but statistically significantly, increased among children who acquire their MMR vaccination.¹⁴ Young men who have previously been exposed to hepatitis virus have less atopy as defined by type I allergies.¹⁵ These findings and others have promoted the hygiene theory, which claims that the immune system is only properly developed if exposed to a majority of the microbial agents normally surrounding us, but less so in industrialized countries with 'clean'

environments thus giving increased room for a Th-2 maturation of the human immune system.¹⁶

The food industry complex

'We are what we eat' is an old saying. Much thought has been put into what food is eaten by infants and how this contributes to food allergy – in particular type I allergy to cow's milk and eggs. These immune reactions can be found in infants. They are significantly more common among infants who develop AE because of the Th-2 skewing of their immune system. Still, the great majority of children with atopic eczema do not have food allergies. Whether chemicals as food preservatives or colouring agents, etc. contribute to atopic eczema is largely unknown. However, environmentalists can document many new chemicals in the food chain over the last 50 years.

Topical steroids

This is a provocative statement without any documentation. But is it prolonging eczema by treating the acute inflammation, then stopping therapy, resulting to a relapse, then treating again, etc? Is this a vicious cycle leading to a progressive, immunological imbalance? It is not known regarding eczema, but the authors have some interesting information from children treated for asthma. Among a group of 206 children with specific type I allergies and hay fever with an increased risk for asthma, half went through hyposensitisation over a 3-year period. The outcome showed that the development of asthma was significantly less in the immunised group.¹⁷ It is my clinical impression – not scientifically documented – that long-term control of eczema will lead to much less disease activity and less demand for therapy

Interventions known to reduce disease severity

Breastfeeding

Breastfeeding and the development of atopic eczema have been extensively studied. A meta-analysis showed many studies could not demonstrate a significant effect, but others did.¹⁸ Recent studies confirm this trend.^{19,20} However, a recent German study again questions if breastfeeding is helpful.²¹

Many consider that breastfeeding is one way of avoiding the development of type I allergy to cow's milk and it is. However, breastfeeding includes so many other important factors for infants. Thus, breastfed infants have a thymus double the size of nonbreastfed children.²² Therefore, the

impact of breastfeeding on the immune system of the infant is huge and is likely to include maturation factors for the establishment of the peripheral T lymphocyte system.

Probiotics

There are now several studies documenting that inclusion of *Lactobacillus rhamnosus* strain GG in the food of pregnant mothers and during breastfeeding significantly reduces or delays outbreak of atopic eczema in children at risk.^{23,24} Also, even a short 1-month diet with addition of probiotics will lead to a significant reduction in itch activity.²⁵ *Lactobacillus* is likely to be very important to the development of gut immunity. How it affects the immune-mediated skin inflammation of atopic eczema is unknown today, but the future should focus on the proper use of probiotics in order to reduce children at risk.²⁶

Interventions with no certain effect on disease severity

Allergen avoidance

The picture is now becoming clearer. Allergen avoidance does not really work. One study suggested that house dust mite (HDM) avoidance reduced eczema activity by approximately 30%.²⁷ Two other studies conducted over a year showed no improvement.^{28,29} A recent study showed improvement, but also in the placebo group.³⁰

An interesting study among newborns is worth mentioning. A large group of children were given occlusive mattress covering during the first 2 years of age and were compared with a nonintervention group of children. Table 3 shows the outcome and the result is very clear: no reduction was found in type I allergy to house dust mite. Children who had no exposure to HDM at the age of 3 months had significantly less atopic eczema. However, within the 2-year observation period, no difference was

Table 3 The table shows a summary of results from an intervention study, where 296 mothers and children had occlusive bed coverings during the first 2 years of life (active group), and 256 mothers and children did not have intervention (placebo) regarding avoiding exposure to house dust mite in their bed environment. When the children reached 2 years of age several parameters were measured²⁹.

	Intervention group	Non-intervention group
Number of children	296	256
Total serum IgE IU/mL	6.83	6.57
Specific IgE against HDM	0.7% of children	0.8% of children
Specific IgE, any allergen	14.4% of children	14.0% of children

Table 4 The Table lists recent studies claiming an effect of milk and egg-avoidance diets on the development of atopic eczema.

Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years' follow-up. <i>Acta Paediatrica</i> 1996; suppl 414: 1–21.	279 high-risk infants were breastfed, avoided cow's milk, mother's smoking, and public day care before age 2. 'Allergic manifestations' were significantly reduced, but associated with increased total serum IgE levels.
Halken S, Host A, Hansen LG, Osterballe O. Prevention of allergy in infants. A prospective study of 159 high-risk children. <i>Ugeskr Laeger</i> 1994; 156: 3789–90.	At 18 months the intervention group children had 14% with eczema compared with 31% in the non-intervention group. The interventions were breastfeeding or hypoallergenic milk formulas, non-smoking and avoidance of furred pets.
Businco L, Bruno G, Giampietro PG, Ferrara M. Is prevention of food allergy worthwhile? <i>J Invest Allergol Clin Immunol</i> 1993; 3: 231–6.	5-year follow-up study in high-risk children. Significant reductions were found regarding atopic eczema, food allergy and asthma at 5 years of age. A genetic predisposition to IgE-mediated reactivity was a prerequisite.

observed in the prevalence of AD.³¹ The only argument against this finding is that it is impossible to avoid contact with HDM – irrespective of occlusive bed coverings. But if so, any allergen avoidance scheme is doomed to fail and not worth the efforts.

Diets

Diets are tried by parents among 75% of children with atopic eczema. When there is a single, specific and very strong type I reaction, e.g. peanuts, then total avoidance is helpful. But all other attempts seem to have failed. There are many reports documenting how the elimination of cow's milk in the diet led to less eczema (see Table 4), but others were not able to confirm these observations.³² As eczema develops at a time when solid food items are introduced to the child, the interest in food and allergy will continue for years. However, Fig. 1 shows the little girl outgrowing her eczema without the need for diets. The boy in Fig. 2 had no effect of a diet, either.

Two large reports on treatment recommendations of atopic eczema are now out. The British conclude on dietary interventions that egg and milk-free interventions in unselected children with eczema are not helpful (Hoare *et al.*; p. 65), and that borage or fish oil supplement is without any effect (Hoare *et al.*; p. 69). The guidelines from the American Academy of Dermatology are in line with the British (Guidelines of Care for Atopic Dermatitis; American Academy of Dermatology) will be published on the internet. <http://www.ncchta.org>

Therapeutic interventions known to reduce disease activity

Emollients

The amount of omega-hydroxy-ceramides and certain free fatty acids are significantly reduced in both lesional

and nonlesional atopic skin.³⁴ This explains why atopics have dry skin as the water evaporation through their skin barrier is increased. Likely, but not proven, the genetic factor(s) in atopic eczema could be linked to the rate-limiting enzymes for skin lipid production.

It has been clearly documented how the routine use of an emollient alone will be able to keep mild to moderate atopic eczema under control for up to 6 weeks among 30% of the children.³⁵ Regular use of emollients is steroid-sparing³⁶ and should be the basic therapy in every eczema patient. Emollients have been shown to prevent dryness and hand eczema in cleaning assistants³⁷ and are very important for anyone having daily physical or chemical stress on their skin.

What is the best emollient? One which is cosmetically acceptable, and has a molar ratio of free fatty acids : ceramides : cholesterol close to 1 : 1 : 1.³⁸

Antihistamines and atopic eczema

These are used very often and certainly help reduce urticarial symptoms, which are commonly involved in AE.⁴ But they do not inhibit eczema inflammation.³⁹ They may do so, if used at an increased dosage. The sedative antihistamines are beneficial, when used at bedtime for children.

Topical steroids

These are still the golden standard and proven beyond any doubt to be very efficacious for disease suppression and control. They are registered for short-term treatment, only. A few open studies have shown that intermittent (three times weekly or twice weekly) application of a topical steroid on previously affected skin will lead to a prolonged remission period – in majority up to 6 months.^{40,41} There seemed to be no clinically visible skin atrophy except in a few patients.

Table 2 contains the argument that the atopic eczema epidemic started when topical steroids became available. It is not unfair to speculate whether the remission – relapse – remission – relapse cycle, arising as a consequence of topical steroid therapy, actually prolongs the course of the disease. It would be hard to prove, but one observation may support the theory that topical steroids are a contributing factor to atopic eczema epidemic. Children in anthroposophic families (i.e. those who do not receive vaccinations, antibiotics, topical steroids, etc.) have significantly less eczema compared with a control group.⁴²

The topical immunomodulators

A novel treatment option is today available for treatment and long-term control of atopic eczema. In very extensive studies, the efficacy and effects from these new compounds are clearly documented. Pimecrolimus equals hydrocortisone acetate 1% as does tacrolimus 0.03%. Tacrolimus 0.1% is equal to hydrocortisone butyrate.^{43,44} The new compounds do not have the side-effects of skin atrophy and can be used for treatment and long-term control of eczema.^{35,43–46} They may have the ability to shorten the course of disease as illustrated in Fig. 2(a,b), but only long-term studies will tell.

Conclusion

Can early intervention change the natural course of atopic eczema? There is no firm data to give a finite answer to this question. Perhaps, probiotics will be the most efficacious remedy in the immediate future. Breast-feeding may be helpful, but the studies are not all in favour of this intervention. Emollients and treatment that can certainly control eczema are very important. But if the availability of a long-term control could change the outlooks for AE children is not yet known. The future will show.

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